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Green and Convenient Synthesis of Polyfunctionalized Piperidines Catalyzed by Ascorbic Acid under Ambient Temperature

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A green and mild synthetic route is introduced to conveniently produce polyfunctionalized piperidines using ascorbic acid as a green and biodegradable catalyst *via* Knoevenagel- intramolecular [4+2] aza-Diels-Alder imin-based reaction in ethanol media. All reactions are completed by a five-component condensation reaction between 1,3-dicarbonyl compounds, aromatic aldehydes, and various amines in a short period of time, and the products are obtained in good to high yields. Using a green, biodegradable and readily available catalyst, a straightforward work-up with no column chromatographic separation, mild reaction conditions, avoidance of toxic organic solvents, and highly efficient and atom-economy process are of the salient features for the proposed approach.

Keywords: Ascorbic acid, Polyfunctionalized piperidines, Green procedure, Ethanol media, Simple work-up

INTRODUCTION

Polyfunctionalized heterocyclic compounds are the building block for many natural products and important synthetic molecules which have a high potential application in the synthetic drugs and biology. Highly substituted piperidines are widely distributed in naturally occurring monocyclic and bicyclic alkaloids and synthetic drugs [1]. Also, piperidine and its derivatives have an important role in drug discovery exhibiting various biological activities such as anti-hypertensive [2], antimalarial [3], neuro-protective [4,5], antibacterial [6], anticonvulstant [7] and anti-inflammatory activities [8]. It is also noteworthy that the substituted piperidines are important therapeutic agents in the treatment of influenza infection [9-11], diabetes [12,13], viral infections including AIDS [14,15] and cancer metastatis [16,17]. Besides, some of the tetrahydropyridine (THP) derivatives have been found to possess enzyme inhibitory activity versus farnesyl transferase [18].

Among the various factors, solvents and catalysts play important roles in green chemistry. In recent years, using green and environmentally friendly catalysts to synthesize the target compounds in the absence of harsh reaction conditions has become a great challenge for researchers. In this respect, multi component reactions (MCRs) [19-24] using green catalysts [25,26] have attracted a great attention in organic and medicinal chemistry.

In view of the great importance of piperidines, recently, the synthesis of these compounds has been reported using multi component reactions in the presence of VCl_3 [27], $BF_3.SiO_2$ [28], Ph_3CCl [29] , $LaCl_3.7H_2O$ [30], tartaric acid [31], iodine [32], $ZrOCl_2.8H_2O$ [33], $ZrCl_4$ [34], $InCl_3$ [35,36], tetrabutylammoniumtribromide (TBATB) [37], $Bi(NO_3)_3.5H_2O$ [38], bromodimethylsulfonium bromide (BDMS) [39], cerium ammonium nitrate (CAN) [40], *p*-toluenesulfonic acid monohydrate (*p*-TsOH·H_2O) [41], Fe@Si-Gu-Prs [42] , $SbCl_3$ [43], glutamic acid [44] and SbI_3 [45]. Although these protocols find certain merits of their own, still they suffer from a number of demerits such as relying on multi-step conditions, use of toxic organic solvents or catalysts containing transition metals, hard work-up procedure, relatively expensive catalysts, troublesome waste discarding and unsatisfactory yields.

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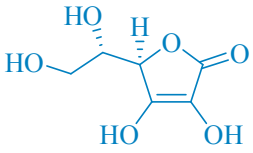
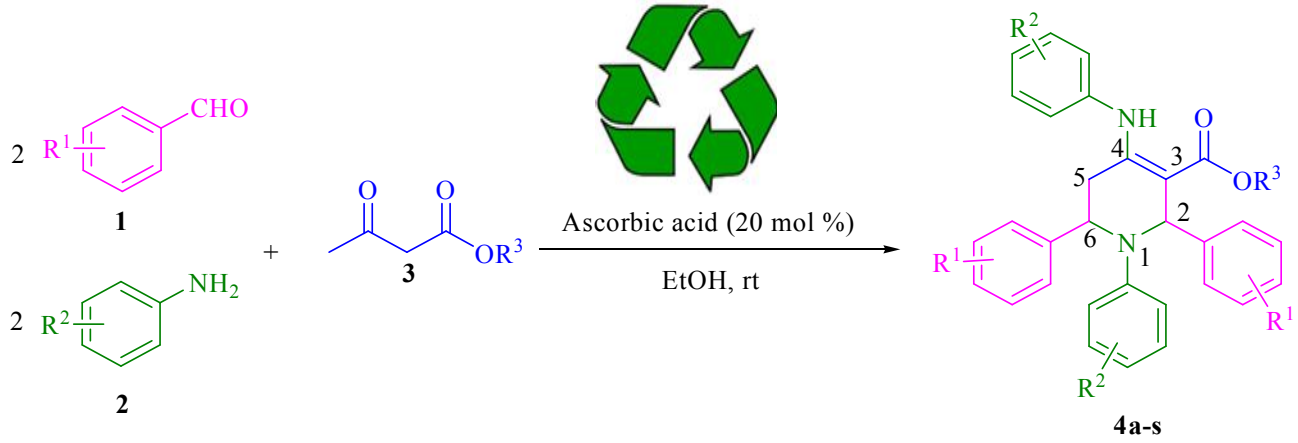


Fig. 1. Structure of ascorbic acid.



Scheme 1. Synthesis of highly substituted piperidine

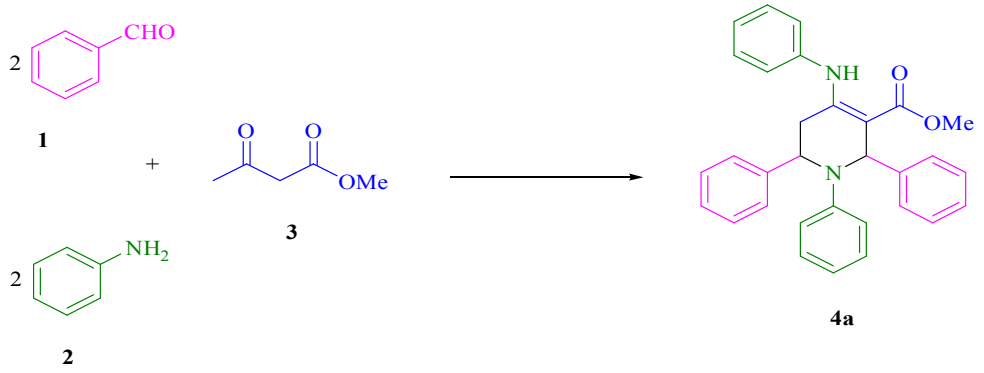
Thus, a search for more general, green, efficient and feasible routes to this class of highly substituted piperidines remains a valid exercise. In recent years, the use of ascorbic acid (Fig. 1) has received a considerable attention in organic chemistry as a catalyst [46] because of its important advantages, such as green, natural, low-cost, high efficiently. It is also well documented that the ascorbic acid has many applications in the pharmacy and food. Because of the antioxidant activities and metabolic functions of ascorbic acid, known as vitamin C, it should be incorporated into the human diet. L-ascorbic acid in plants, the main source of vitamin C for humans, is also among the essential compounds for plants, with important roles as an antioxidant and as a modulator of plant development through hormone signaling [47].

Here, we report a green and convenient protocol for preparation of highly substituted piperidines *via* a five-component reaction between aromatic aldehydes, anilines, and *β*-ketoesters in the presence of catalytic amount of ascorbic acid as a catalyst in ethanol at ambient temperature (Scheme 1).

RESULTS AND DISCUSSION

To optimize the reaction conditions, we evaluated the catalyst activity of ascorbic acid for the synthesis of highly substituted piperidines. At first, catalytic activity of ascorbic acid was tested in a model system in a multi-component reaction between a mixture of benzaldehyde (2 mmol), aniline (2 mmol) and methyl acetoacetate (1 mmol). In the absence of a catalyst, no product was obtained at r.t. and 50 °C for a reaction time of about 24 h (Table 1, entries 1 and 2) indicating the necessity of a catalyst for this transformation. The optimized conditions were determined by changing the effecting parameters on the reaction such as amount of the catalyst, solvent and the temperature. Thereafter, for determining the optimum quantity of catalyst, the model reaction was performed in the presence of different amounts of ascorbic acid. Various loadings of catalyst, including 5, 10, 15, 20 and 25 mol% were screened in our model reaction. By lowering the catalyst loading to 5 mol%, the corresponding product was obtained in lower yield (Table 1, entry 3). By increasing the amount of

Table 1. Optimization of the Reaction Condition in the Synthesis 4a[a]



Entry	Ascorbic acid (mol %)	Solvent	Time (h)	Isolated yields (%)
1	Catalyst free	EtOH	24	Not product
2	Catalyst free	EtOH, 50 °C	24	Not product
3	5	EtOH	24	26
4	10	EtOH	18	48
5	15	EtOH	14	71
6	20	EtOH	11	86
7	20	EtOH, 50 °C	9	72
8	20	H_2O	18	trace
9	20	Solvent free	18	34
10	20	Solvent free, 50 °C	14	27
11	20	CH_2Cl_2	24	29
12	20	MeOH	14	65
13	20	$CHCl_3$	24	23
14	20	CH_3CN	18	38
15	25	EtOH	11	87

[a]Reaction conditions: benzaldehyde (2 mmol), aniline (2 mmol), methyl acetoacetate (1 mmol), and catalyst in various solvents and temperatures.

catalyst from 5 to 10, 15 and 20 mol%, the reaction time was reduced and the yield of the product increased (Table 1, entries 3-6). On the basis of the optimization results, 20 mol% of ascorbic acid was considered as the most efficient catalyst for this reaction (Table 1, entry 6). We also examined the influence of temperature on the reaction yield.

Despite the short reaction time for ascorbic acid (20 mol%) at 50 °C the yield of the corresponding product was low (72%) (Table 1, entry 7). The larger amount of the catalyst did not improve the yield (Table 1, entry 15). In the absence of solvent and in the presence of 20 mol% catalyst, at r.t. and 50 °C, the reaction was investigated, which resulted in the production of a reaction product with low yield and longer reaction time, indicating that the solvent plays an effective role in the development of this reaction (Table 1, entries 9, 10). Therefore, choosing an appropriate solvent is of a particular importance in the successful synthesis. To search for the optimal solvent, the model reaction was investigated in the presence of 20 mol% of ascorbic acid using various solvents. The results indicated that a low yield of the desired product is obtained when H_2O, CH_2Cl_2, MeOH, $CHCl_3$ and CH_3CN were used as solvents. The best yield was obtained when the reaction was performed in EtOH and it accelerated the reaction compared with other solvents and solvent-free condition. The results of these comparative experiments are summarized in Table 1. Therefore, we employed the optimized conditions under 20 mol% of ascorbic acid as a catalyst in EtOH at rt for the condensation reaction of aromatic aldehydes (1, 2 mmol) and amines (2, 2 mmol) and methyl/ethyl acetoacetate (3, 1 mmol) into the corresponding highly substituted piperidines (Scheme 1 and Table 2). Encouraged by the remarkable results obtained from the above conditions, and in order to show the generality and scope of this protocol, we used various aromatic aldehydes and amines bearing either electron-withdrawing functional groups or electron-donating groups for the synthesis of corresponding highly substituted piperidines. The effects of substituents on the aromatic rings were found to be strong in terms of yields under these reaction conditions. Both classes of aromatic aldehydes and amines containing electron-releasing and electronwithdrawing substituents in their aromatic rings gained the appropriate products in good to high yields and short reaction times. We also applied methyl/ethyl acetoacetate. In each of these substitutions, there is no significant difference in the reaction rate and product yields. The results are summarized in Table 2.

The proposed mechanistic routes for the synthesis of highly substituted piperidines in the presence of ascorbic acid are shown in Scheme 2. At first, condensation of aromatic aldehyde 1 and *β*-ketoester 3 with amine 2 in the presence of ascorbic acid was performed to produce enamine A and imine B. Then, enamine A was reacted with imine B to produce intermediate C through intermolecular Mannich-type reaction. The reaction between intermediate C and aldehyde 1 led to intermediate D. Next, tautomerization of D generated intermediate E, which immediately underwent intramolecular Mannich-type reaction to give intermediate F. Eventually, the intermediate F was tautomerized to generate the desired piperidine derivative 4 due to conjugation with the ester group (Scheme 2).

Comparison of catalytic ability of some catalysts reported in the literature for the synthesis of highly substituted piperidines is shown in Table 3. This study reveals that ascorbic acid has an extraordinary potential to be an alternative green, biodegradable and cost effective catalyst for the synthesis of these biologically active heterocyclic compounds with good to high yields and short reaction times.

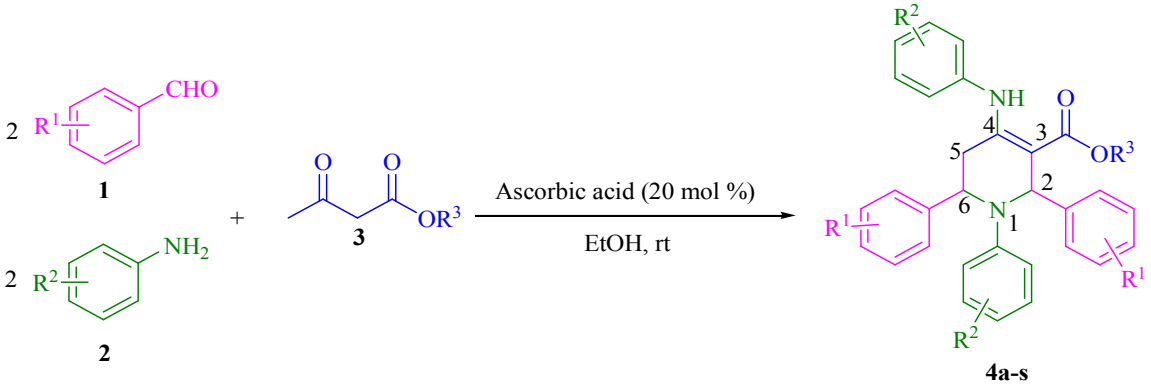
EXPERIMENTAL

Melting points and IR spectra of the compounds were determined using an Electro thermal 9100 apparatus and a JASCO FTIR 460 Plus spectrometer. Also, nuclear magnetic resonance, ^{1}H NMR spectra were recorded on a Bruker DRX-400 Avance instruments with $CDCl_3$ as a solvent. All reagents and solvents were purchased from Merck, Fluka and Acros chemical companies, and used without further purification.

General Procedure for the Synthesis of Highly Functionalized Piperidine (4a-s)

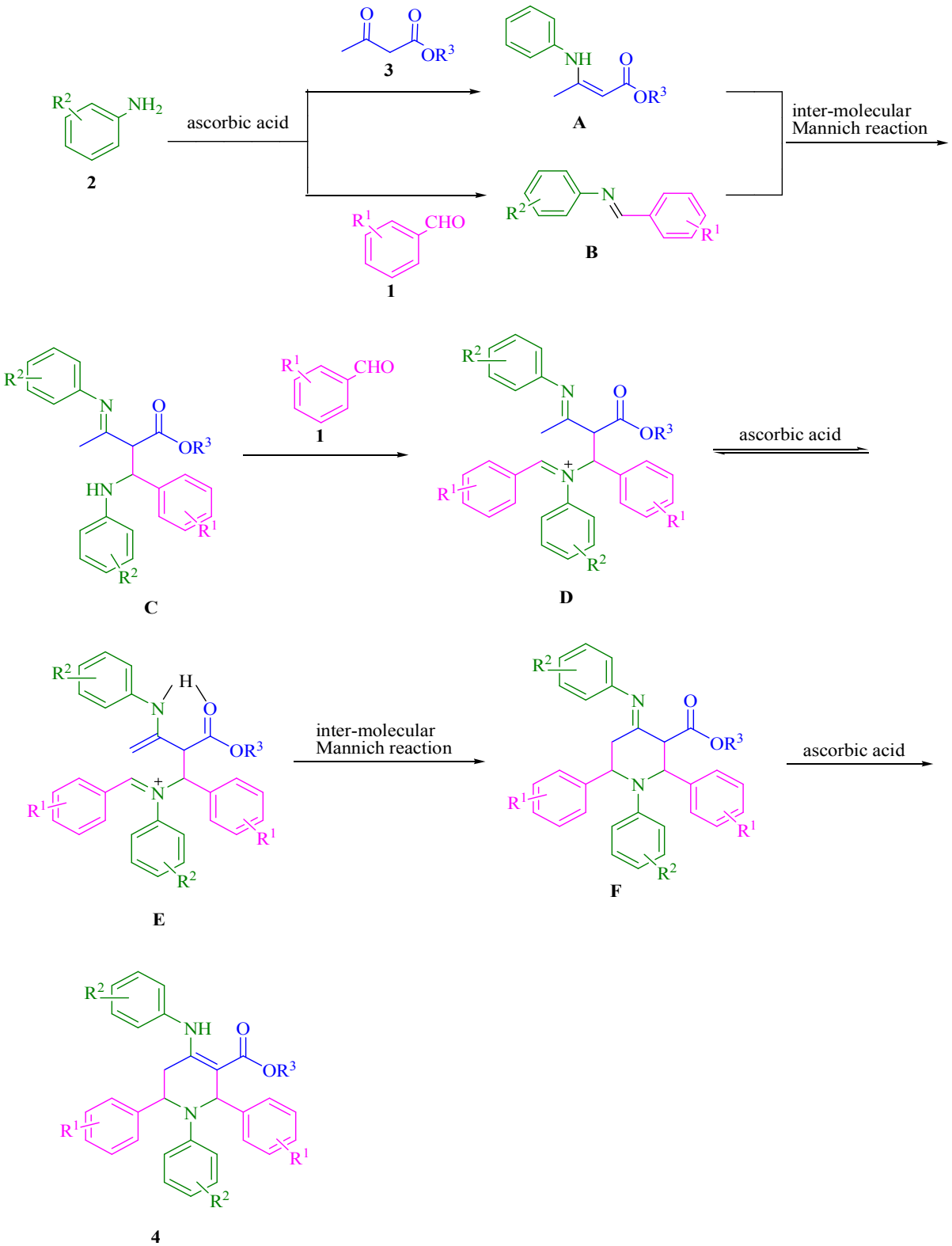
A solution of aromatic amine 2 (2.0 mmol) and *β*-ketoester 3 (1.0 mmol) in EtOH (5 ml) was stirred for 20 min in the presence of 20 mol% ascorbic acid at room temperature. Next, the aromatic aldehyde 1 (2.0 mmol) was added and the reaction mixture was stirred for the time indicated in Table 2. The progress of the reaction was monitored by thin-layer chromatography (TLC: n-hexane/ethyl acetate (3:1)). After completion of the reaction, the thick precipitate was filtered off and washed with ethanol (3 × 2 ml) to give the pure product 4. Products were

Table 2. Synthesis of Highly Substituted Piperidines



Entry	R^1	R^2	R^3	Product	Time (h)	Yield (%)[a]	M.p. (°C)	Lit. M.p. (°C)
1	H	H	Me	4a	11	86	170-172	169-171[34]
2	H	H	Et	4b	11	84	174-176	173-175[34]
3	H	4-Me	Et	4c	8	88	195-197	196-198[38]
4	H	4-Cl	Et	4d	12	82	205-207	203-205[34]
5	4-OMe	H	Me	4e	10	85	187-189	187-188[39]
6	4-OMe	4-Cl	Me	4f	14	79	194-196	194-195[40]
7	4-OMe	H	Et	4g	10	84	167-169	166-168[34]
8	4-NO_2	H	Me	4h	9	83	241-243	239-241[32]
9	4-NO_2	H	Et	4i	9	85	246-248	247-250[40]
10	4-Me	H	Me	4j	8	87	214-216	212-214[39]
11	4-Me	4-F	Me	4k	7	89	197-199	199-201[29]
12	4-Me	4-F	Et	4l	7	86	187-189	186-187[31]
13	4-Me	4-Cl	Et	4m	9	82	220-222	218-220[28]
14	4-Me	4-Br	Et	4n	11	79	232-234	234-236[28]
15	4-Me	3,4-Cl_2-C_6H_3	Et	4o	13	76	174-176	173-175[41]
16	4-Br	4-Cl	Me	4p	14	74	163-165	160-163[33]
17	4-F	H	Me	4q	7	88	179-181	180[41]
18	4-F	4-Me	Me	4r	9	87	202-204	203-205[31]
19	4-Cl	H	Me	4s	8	83	188-190	189-191[39]

[a]Isolated yield.



Scheme 2. Proposed mechanistic route for the synthesis of highly substituted piperidines

Table 3. Comparison of Catalytic Ability of some Catalysts Reported in the Literature for the Synthesis of Piperidines[a]

Entry	Catalyst	Conditions	Time/Yield (%)	Ref.
1	Ph_3CCl	MeOH, 50 °C	5 h/79	[29]
2	Tartaric acid	MeOH, r.t.	14 h/79	[31]
3	I_2	MeOH, r.t.	8 h/81	[32]
4	$ZrOCl_2.8H_2O$	EtOH, reflux	3.5 h/80	[33]
5	$ZrCl_4$	EtOH, r.t.	9 h/90	[34]
6	$InCl_3$	CH_3CN, r.t.	24 h/60	[35]
7	TBATB	EtOH, r.t.	24 h/74	[37]
8	$Bi(NO_3)_3.5H_2O$	EtOH, r.t.	12 h/81	[38]
9	BDMS	CH_3CN, r.t.	3 h/75	[39]
10	CAN	CH_3CN, r.t.	20 h/82	[40]
11	*p*-TsOH·H_2O	EtOH, r.t.	10 h/78	[41]
12	Ascorbic acid	EtOH, r.t.	11 h/86	This work

[a]Based on the five-component reaction of benzaldehyde (2 mmol), aniline (2 mmol), and methyl acetoacetate (1 mmol).

characterized by comparison of spectroscopic data (^{1}H NMR). Spectra data of products are represented below:

Methyl-1-phenyl-4-(4-chlorophenylamino)-2,6-bis(4-methoxyphenyl)-1,2,5,6-tetrahydropyridine-3-carboxylate (4f). Yield: 79%; m. p.: 194-196 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.71 (1H, dd, *J* = 15.2, 2.4 Hz, H′-5), 2.86 (1H, dd, *J* = 15.2, 5.6 Hz, H″-5), 3.81, 3.83, 3.97 (9H, 3s, 3OCH_3), 5.07 (1H, d, *J* = 3.6 Hz, H-6), 6.28 (2H, d, *J* = 8.0 Hz, ArH), 6.32 (1H, s, H- 2), 6.46 (2H, d, *J* = 8.0 Hz, ArH), 6.83-7.20 (12H, m, ArH), 10.25 (1H, s, NH).

Methyl-1-phenyl-4-(phenylamino)-2,6-bis(4-methylphenyl)-1,2,5,6-tetrahydropyridine-3-carboxylate (4j). Yield: 87%; m. p.: 214-216 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.25 (3H, s, CH_3), 2.32 (3H, s, CH_3), 2.75 (1H, dd, *J* = 15.2, 2.4 Hz, H′-5), 2.84 (1H, dd, *J* = 15.2, 5.6 Hz, H″-5), 3.93 (3H, s, OCH_3), 5.09 (1H, d, *J* = 3.1 Hz, H-6), 6.32 (2H, d, *J* = 8.0 Hz, ArH), 6.37 (1H, s, H-2), 6.48 (2H, d, *J* = 8.8 Hz, ArH), 6.60 (1H, t, *J* = 7.2 Hz, ArH), 7.00-7.12 (11H, m, ArH), 7.20 (2H, d, *J* = 8.0 Hz, ArH), 10.29 (1H, s, NH).

Methyl-4-(4-fluorophenylamino)-1-(4-fluorophenyl)-1,2,5,6-tetrahydro-2,6-diptolylpyridine-3-carboxylate (4k). Yield: 89%; m. p.: 197-199 °C; IR (KBr) ν = 3255 (NH), 1649 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.36 (s, 3H, CH_3), 2.38 (s, 3H, CH_3), 2.66 (dd, 1H, *J* = 15.1, 2.8 Hz, H′-5), 2.86 (dd, 1H, *J* = 15.1, 6.0 Hz, H″-5), 3.95 (s, 3H, OCH_3), 5.08 (d, 1H, *J* = 4.0 Hz, H-6), 6.25-6.28 (m, 2H, ArH), 6.33 (s, 1H, H-2), 6.43-6.48 (m, 2H, ArH), 6.77-6.84 (m, 4H, ArH), 7.05-7.20 (m, 8H, ArH), 10.17 (s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 21.0 (CH_3), 21.1 (CH_3), 33.6 (C-5), 51.0 (OCH_3), 55.4 (C-2), 58.1 (C-6), 98.0 (C-3), 113.6 (d, *J* = 7.0 Hz), 115.2 (d, *J* = 22.0 Hz), 115.6 (d, *J* = 22.0 Hz), 126.4 (d, *J* = 23.0 Hz), 128.0 (d, *J* = 8.0 Hz), 129.0, 129.4, 133.9 (d, *J* = 3.0 Hz), 136.0, 136.9, 139.7, 140.6, 143.5, 155.0 (d, $^1J_{CF}$ = 233.0 Hz), 156.2 (C-4), 160.7 (d, $^1J_{CF}$ = 244.0 Hz), 168.6 (C=O).

Ethyl-4-(4-bromophenylamino)-1-(4-bromophenyl)-1,2,5,6-tetrahydro-2,6-diptolylpyridine-3-carboxylate (4n). Yield: 79%; m. p.: 232-234 °C; IR (KBr) ν = 3310 (NH), 1652 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.49 (t, 3H, *J* = 6.8 Hz, OCH_2CH_3), 2.35 (s, 3H, CH_3), 2.38 (s, 3H, CH_3), 2.74 (d, 1H, *J* = 15.2 Hz, H′-5), 2.88 (dd, 1H, *J* = 15.2, 5.6 Hz, H″-5), 4.33-4.39 (m, 1H, OCH_aH_b), 4.45–4.51 (m, 1H, OCH_aH_b), 5.09 (d, 1H, *J* = 3.6 Hz, H-6), 6.17 (d, 2H, *J* = 8.0 Hz, ArH), 6.35 (s, 1H, H-2), 6.42 (d, 2H, *J* = 8.8 Hz, ArH), 7.05-7.24 (m, 12H, ArH), 10.26 (s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 14.7 ($OCH_2\underline{CH_3}$), 21.0 (CH_3), 21.2 (CH_3), 33.4 (C-5), 55.0 (C-2), 58.1 (C-6), 59.9 (OCH_2CH_3), 99.0 (C-3), 108.2, 114.5, 118.9, 126.2, 126.4, 127.2, 129.0, 129.4, 131.5, 131.9, 136.1, 137.0, 139.1, 140.2, 146.0, 155.2 (C-4), 168.1 (C=O).

Ethyl-4-(3,4-dichlorophenylamino)-1-(3,4-dichlorophenyl)-2,6-bis(4-methylphenyl)-1,2,5,6-tetrahydro-2,6-diptolylpyridine-3-carboxylate (4o). Yield: 76%; m. p.: 174-176 °C; IR (KBr) ν = 3301 (NH), 1660 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 1.50 (t, 3H, *J* = 6.4 Hz, OCH_2CH_3), 2.34 (s, 3H, CH_3), 2.35 (s, 3H, CH_3), 2.73 (d, 1H, *J* = 15.2 Hz, H′-5), 2.90 (dd, 1H, *J* = 15.2, 5.6 Hz, H″-5), 4.31-4.40 (m, 1H, OCH_aH_b), 4.46–4.54 (m, 1H, OCH_aH_b), 5.08 (br s, 1H, H-6), 6.15 (d, 2H, *J* = 7.2 Hz, ArH), 6.36 (s, 1H, H-2), 6.42 (d, 2H, *J* = 7.6 Hz, ArH), 6.95-7.25 (m, 10H, ArH), 10.24 (s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 14.8 ($OCH_2\underline{CH_3}$), 21.6 (CH_3), 21.8 (CH_3), 33.4 (C-5), 55.3 (C-2), 58.3 (C-6), 59.8 (OCH_2CH_3), 98.9 (C-3), 108.3, 114.6, 119.1, 123.5, 123.5, 126.9, 127.2, 127.4, 127.4, 128.2, 128.2, 128.7, 131.5, 131.9, 137.0, 138.0, 138.4, 142.2, 143.3, 146.0, 155.3 (C-4), 168.1 (C=O).

Methyl-4-(4-methylphenylamino)-1-(4-fluorophenyl)-1-(4-methylphenyl)-1,2,5,6-tetrahydro-2,6-diptolyl-pyridine-3-carboxylate (4r). Yield: 87%; m. p.: 202-204 °C; IR (KBr) ν = 3264 (NH), 1658 (C=O) cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.20 (s, 3H, CH_3), 2.31 (s, 3H, CH_3), 2.75 (dd, 1H, *J* = 15.1, 2.4 Hz, H′-5), 2.83 (dd, 1H, *J* = 15.1, 5.6 Hz, H″-5), 3.95 (s, 3H, OCH_3), 5.11 (br s, 1H, H-6), 6.31 (d, 2H, *J* = 8.4 Hz, ArH), 6.37 (s, 1H, H-2), 6.42 (d, 2H, *J* = 8.8 Hz, ArH), 6.92 (d, 2H, *J* = 8.4 Hz, ArH), 7.97-7.02 (m, 6H, ArH), 7.12-7.15 (m, 2H, ArH), 7.27-7.31 (m, 2H, ArH), 10.22 (s, 1H, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm): 20.1 (CH_3), 33.7 (C-5), 51.0 (OCH_3), 54.7 (C-2), 57.3 (C-6), 97.2 (C-3), 113.0, 114.9 (d, *J* = 21.0 Hz), 115.4 (d, *J* = 21.0 Hz), 125.6, 125.8, 127.9 (d, *J* = 8.0 Hz), 128.2 (d, *J* = 7.0 Hz), 129.6, 135.0, 135.9, 138.4, 139.7, 144.5, 156.4 (C-4), 161.5 (d, $^1J_{CF}$ = 243.0 Hz), 161.9 (d, $^1J_{CF}$ = 244.0 Hz), 168.4 (C=O).

Methyl--1-phenyl-4-(phenylamino)-2,6-bis(4-chlorophenyl)-1,2,5,6-tetrahydropyridine-3-carboxylate (4s). Yield: 83%; m. p.: 188-190 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.75 (1H, dd, *J* = 15.2, 2.4 Hz, H′-5), 2.86 (1H, dd, *J* = 15.2, 5.6 Hz, H″-5), 3.94 (3H, s, OCH_3), 5.11 (1H, d, *J* = 3.6 Hz, H-6), 6.39 (2H, d, *J* = 7.8 Hz, ArH), 6.40 (1H, s, H-2), 6.56 (2H, d, *J* = 8.0 Hz, ArH), 6.64 (1H, t, *J* = 7.0 Hz, ArH), 7.04-7.27 (13H, m, ArH), 10.26 (1H, s, NH).

CONCLUSIONS

We have introduced ascorbic acid as a green, highly efficient and biodegradable catalyst, for the convenient and mild synthesis of highly substituted piperidines *via* multi-component reaction between aromatic aldehydes, anilines and *β*-ketoesters in ethanol media. Use of green, highly efficient and readily available catalyst, simple and cleaner reaction profile, good to high yields and short reaction times besides the ethanol media, simple purification of products, absence of hazardous organic solvents provides a good example of a competitive alternative synthetic methodology to prepare these biologically active compounds.

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